Pain hypersensitivity

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Pain systems need to be sensitive enough to detect potentially harmful stimuli. But often they become too sensitive, causing us pain that provides no benefit. This hypersensitivity arises because our pain pathways actually increase in sensitivity when they relay pain messages, and the mechanisms of this sensitization are beginning to be revealed.

Normally, pain is produced only by intense stimuli that are potentially or actually damaging to tissue (technically known as noxious stimuli, although commonly referred to as pain stimuli). This pain is mediated by a specific system of high-threshold peripheral and central neurons designed to respond only to such noxious stimuli (the nociceptive system, also see Sensing damage), which is responsible for the 'ouch' pain we experience in response to a needle prick or on touching a hot surface.

Nociceptive pain is an essential early warning device that helps protect us from the dangerous environment we find ourselves in. To do this the sensation of pain needs to be so unpleasant that we cannot ignore it.

Clinical pain, by contrast, occurs in response to tissue injury and inflammation (inflammatory pain), damage to the nervous system (neuropathic pain) and alterations in the normal function of the nervous system (functional pain). It features both spontaneous pain that arises without any apparent peripheral stimulus and hypersensitivity to peripheral stimuli.

Pain hypersensitivity takes two forms:

- thresholds are lowered so that stimuli that would normally not produce pain now begin to (alldynia).

- responsiveness is increased, so that noxious stimuli produce an exaggerated and prolonged pain (hyperalgesia).

Pain hypersensitivity after an injury helps healing by ensuring that contact with the injured tissue is minimized until repair is complete – an adaptive response. However, pain hypersensitivity may persist long after an injury has healed or occur in the absence of any injury. In this case, pain provides us with no benefits, and is a manifestation of pathological change in the nervous system.

What produces pain hypersensitivity and how can we normalize it? Two mechanisms are known to be involved: peripheral and central sensitization. 'Sensitization' here means an increase in the excitability of neurons, so they are more sensitive to stimuli or sensory inputs.
Peripheral sensitization

Peripheral sensitization is a reduction in threshold and an increase in responsiveness of the **peripheral ends of nociceptors**, the high-threshold peripheral sensory neurons that transfer input from peripheral targets (skin, muscle, joints and the viscera) though peripheral nerves to the central nervous system (spinal cord and brainstem).

Peripheral sensitization contributes to the pain hypersensitivity found at the site of tissue damage and inflammation. A good example of this is the change in heat sensitivity after sunburn, when a normally warm stimulus such as a shower feels burning hot in the sunburned areas.

Sensitization arises due to the action of **inflammatory chemicals** or mediators released around the site of tissue damage or inflammation. Some of these, such as ATP, can **directly activate** the ends of the peripheral nociceptors, signalling the presence of inflamed tissue and producing pain. Other chemical mediators are produced by **activated inflammatory cells**, such as neutrophils (a type of white blood cell). When activated, these cells begin making an enzyme known as Cox-2, which leads to the production and secretion of **prostaglandin PGE2**. This mediator acts as a sensitizer, altering pain sensitivity by increasing the responsiveness of peripheral nociceptors. Aspirin-like pain-killing drugs act by inhibiting Cox-2 and prostaglandin production.

Central sensitization

Central sensitization is an increase in the excitability of neurons within the central nervous system, so that normal inputs begin to produce abnormal responses.

The increased excitability is typically triggered by a burst of activity in nociceptors (such as that evoked by an injury), which **alter the strength of synaptic connections** between the nociceptor and the neurons of the spinal cord (so-called activity-dependent synaptic plasticity).

Low-threshold sensory fibres activated by very light touch of the skin, for example, begin to activate neurons in the spinal cord (for inputs from the body) or in the brainstem (for inputs from the head) that normally only respond to noxious stimuli. As a result, an input that would normally evoke an innocuous sensation now produces pain. In effect, the synaptic changes increase the 'gain' of the system.

Although the pain feels as if it originates in the periphery, it is actually a manifestation of abnormal sensory processing within the central nervous system.

Central sensitization is responsible for **tactile allodynia** (pain in response to light brushing of the skin) and for the spread of pain hypersensitivity beyond an area of tissue damage so that adjacent non-damaged tissue is tender. Central sensitization can also occur after **surgery**, contributing to pain on movement or touch, in **migraine attacks** where brushing hair is often painful, and in some patients with **nerve damage** where even blowing on the skin produces excruciating burning pain.
More recently, it has been suggested that diseases such as **fibromyalgia** (a condition associated with a tender painful muscular pain) or **irritable bowel syndrome** may be manifestations not of peripheral pathology but of altered function of the nervous system (functional pain).

What are the mechanisms responsible for peripheral and central sensitization? At a cellular level they are quite different, but at a molecular level they share several similarities.

**Mechanisms: peripheral sensitization**
Peripheral sensitization is the result of changes in key proteins and ion channels (known as **transduction proteins**) that determine the excitability of the nociceptor terminal. The transduction proteins are the means by which a noxious stimulus, for example excessive heat, is converted into electrical activity. Normally for heat this only occurs at around 42°C, the heat pain threshold. After peripheral inflammation, though, the threshold falls considerably.

Two processes have been implicated in this increase in sensitivity:

- changes to existing nociceptor proteins (**post-translational processing**)  
- changes to the proteins being made by the nociceptor (**altered gene expression**).

Post-translational changes usually involve the **addition of phosphate groups** to some of the protein's amino acids, by enzymes known as kinases. This phosphorylation can dramatically alter the properties of a protein, for example reducing the temperature required to open an ion channel. Sodium ion channels that determine the excitability of the nociceptor terminal can also be phosphorylated. As well as lowering the threshold at which they open, phosphorylation also makes the channel open for longer, so that any stimulus to the terminal will evoke a greater response.

The kinases are activated by a **cascade of intracellular signals** initiated by inflammatory mediators (such as prostaglandins) acting on receptors present on the peripheral ends of the nociceptor. Most of these signals act locally in the terminal to change the properties of proteins present on the membrane.

Some signals, however, are transported from the terminal along the **axon** or nerve fibre to the **cell body** of the sensory neurons in the **dorsal root ganglion**. Here they either change transcription (increase expression of particular genes) or increase translation (ensure more protein is produced from messenger RNA). The increased protein is then shipped back down to the terminal where it contributes to an increased responsiveness of the terminal to peripheral stimuli. One example is the **TRPV1 protein**, an ion channel that responds to heat stimuli. Activation of kinases takes minutes, changes in protein levels a day or so.

**Central mechanisms**
Central sensitization also has two phases:

- an immediate but relatively transient phase; and
● a slower onset but longer-lasting phase.

Again, the first phase depends on changes to existing proteins while the second phase relies on new gene expression.

The early phase reflects changes in synaptic connections within the spinal cord, after a signal has been received from nociceptors. The central terminals of the nociceptor release a host of signal molecules, including the excitatory amino acid synaptic transmitter glutamate, neuropeptides (substance P and CGRP) and synaptic modulators including BDNF.

These transmitters/modulators act on specific receptors on the spinal cord neurons, activating intracellular signaling pathways that lead to the phosphorylation of membrane receptors and channels, particularly the NMDA and AMPA receptors for the glutamate neurotransmitter. These post-translational changes lower the threshold and opening characteristics of these channels, thereby increasing the excitability of the neurons.

A later transcription-dependent phase of central sensitization is mediated by increased levels of protein production. The net effect of these changes is that normally subliminal inputs begin to activate the neurons and pain sensibility is drastically altered.

Among the proteins mediating this effect are dynorphin, an endogenous opioid that increases neuronal excitability, and Cox-2, the enzyme that produces prostaglandin E2. As well as being involved in peripheral sensitization, prostaglandins also affect central neurons, contributing to central sensitization. Indeed, the analgesic action of aspirin-like drugs may derive more from their central than peripheral actions on Cox-2.

**Therapeutic leads**
The increased responsiveness of peripheral and central neurons plays the major role in the production of abnormal pain. The molecular components of the intracellular signalling cascades responsible for sensitization are key targets for new interventions aimed at reducing such pain. Many promising therapies are being tested, based on small drug molecules that interfere with the action of these newly discovered targets.

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**Further reading**


